REMARKS

Claims 19, 21-28, 63-78, 90, 92-103, 105-114, and 117-149 are pending upon entry of the above amendments. Claims 24-26, 28, 64-68, 70, 72, 74, 76, 78, 90, 92, 95-100, 102, 103, and 105-113 have been amended in order to clarify the claimed invention and new claims 127-149 have been added. Support for the claim amendments and the new claims may be found in the specification. Specifically, examples of support for the amendments to claims 24, 95, and 108 can be found on page 8, lines 9-14 of the instant specification. Examples of support for the amendments to claims 25, 26, 65, 66, 96, 97, 109, and 110 can be found on page 9, line 14, to page 10, line 9 of the instant specification. Examples of support for the amendments to claims 28, 78, 99 and 112 can be found on page 8, line 19, to page 9, line 2 of the instant specification. Examples of support for the amendments to claims 64, 67, 68, 70, 72, 74, 76, and 90 can be found on page 10, lines 10-12; page 12, lines 8-12; page 14, line 22, to page 15, line 2; page 16, lines 12-15; and page 18, lines 9-11 of the instant specification. Examples of support for the amendments to claim 92 can be found on page 12, lines 8-14 of the instant specification. Examples of support for the amendments to claim 98 can be found on page 13, lines 10-14 of the instant specification. Examples of support for the amendments to claim 100 can be found on page 10, lines 10-13 and page 12, lines 8-12. Examples of support for the amendment to claim 102 can be found on page 10, lines 13-14 of the instant specification. Examples of support for the amendments to claims 103 and 105-112 can be found on page 15, lines 5-7. Examples of support for the amendment to claim 113, and for new claims 127 and 128 can be found on page 12, lines 8-12; page 14, line 22, to page 15, line 2; page 16, lines 12-15; and page 18, lines 9-11 of the instant specification. Examples of support for claim 129 can be found on page 11, lines 1-2 of the instant specification. Examples of support for claim 130 can be found on page 18, lines 14-17 of the instant specification. Examples of support for claim 131 can be found on page 5, line 20 to page 6, line 2, and page 11, lines 1-9. Examples of support for claim 132 can be found on page 12, lines 2-6 of the instant specification. Examples of support for claim 133 can be found on page 11, lines 1-18 and page 12, lines 6-7 of the instant specification. Examples of support for claim 134 can be found on page 18, lines 12-17 of the instant specification. Examples of support for claim 135 can be found on page 15, lines 5-21 of the instant specification. Examples of support for claim 136 can be found on page 14, lines 17-22 of the instant specification. Examples of support for claims 137 -138 can be found on page 18, lines 3-5 of the instant specification. Examples

of support for claim 139 can be found on page 16, lines 12-15 of the instant specification. Examples of support for claims 140 and 142 can be found on page 13, lines 18-19 and page 16, lines 12-15 of the instant specification. Examples of support for claim 141 can be found on page 13, lines 18-19, page 16, lines 12-15, and page 18, lines 3-5 of the instant specification. Examples of support for claim 143 can be found on page 13, lines 18-21 of the instant specification. Examples of support for claim 144 can be found on page 13, lines 18-21 and page 18, lines 14-17 of the instant specification. Examples of support for claim 145 can be found on page 16, lines 12-15 and page 18, lines 3-5 of the instant specification. Examples of support for claim 146-149 can be found on page 19, lines 15-16 and page 20, lines 6-7 of the instant specification. Thus, the new claims are fully supported by the instant specification and no new matter has been introduced. Thus, the amended claims and the new claims are fully supported by the instant specification and no new matter has been introduced.

Applicant notes that the labeling of steps (1) and (2) in claims 64, 67, 68, 70, 72, 74, 76, and 90 is provided solely for clarity of reading and in no way limits the order of performance of the recited steps. In other words, step (2) can be performed before, after or concurrently with step (1).

New claims 129-149 are intended to correspond exactly or substantially to claims 1-29 of U.S. Patent Application Publication No. 2003/0161834, published August 28, 2003.

As noted in the Amendment filed April 8, 2004, claims 117-126 are intended to correspond exactly or substantially to claims 1-15 of U.S. Patent No. 6,544,518 B1.

Interview Summary

Applicant and her representatives thank Examiner Wilson and Supervisory Patent Examiner ("SPE") Amy Nelson for the courtesies extended during the interview with Drs. Charlotte Kensil, Lauren Foster, Adriane Antler, Reg. No. 32,605, and Mei Benni, Reg. No. 45,470, on March 16, 2004.

During the interview, the rejections and contentions made in the Office Action dated October 27, 2003 were discussed. Dr. Kensil explained why the genus of immunostimulatory oligonucleotides containing at least one unmethylated CpG dinucleotide ("CpG oligonucleotides") and the genus of saponins derived from *Quillaja saponaria* possessing immune adjuvant activity ("QS saponins") are reasonably expected to display synergy in immune adjuvant activity when used together. Both Examiner Wilson and Examiner Nelson agreed that Dr. Kensil presented compelling evidence that synergy in

immune adjuvant activity is a general attribute of the genus of CpG oligonucleotides and the genus of QS saponins. SPE Nelson indicated that the burden now shifted to the Examiner to prove otherwise. Dr. Antler discussed the case law standing for the proposition that post-filing date evidence may be used to show unexpected properties of an invention, and SPE Nelson agreed that applicant may submit post-filing data, such as data obtained using oligonucleotide 2006 (a CpG oligonucleotide which was not available at the time of filing of the application), to show synergy of CpG oligonucleotides with QS saponins in immune adjuvant activity.

Examiner Wilson agreed with the Applicant that Figure 1 of Weiner *et al.*, Proc. Natl. Acad. Sci. USA 94:10833-10873 (1997) ("Weiner", see Exhibit 4 attached to Dr. Kensil's Declaration) demonstrated that two CpG oligonucleotides, oligonucleotide 1643 and oligonucleotide 1758, had an immunostimulatory effect, while oligonucleotide 1812, which is not a CpG oligonucleotide, did not show an immunostimulatory effect. Furthermore, Examiner Wilson agreed with the Applicant that U.S. Patent No. 5,968,909 ("Agrawal", see Exhibit 12 attached to Dr. Kensil's Declaration) did not show that CpG oligonucleotides can be used to reduce the immune response to the oligonucleotides; rather, it teaches how to modify certain phosphorothioate oligonucleotides so that they are less immunostimulatory than the unmodified phosphorothioate oligonucleotides. In response to remarks made by Applicant and her representatives, SPE Nelson also indicated that "chemically modified" probably could not properly be broadly construed to have the meaning of "purified."

Examiner Wilson indicated that he would withdraw the rejection under 35 U.S.C. § 112, first paragraph, that the specification does not support administering a nucleic acid sequence encoding an antigen if the Applicant can point out where the specification supports that (1) an antigen can be a nucleic acid encoding an antigenic protein or peptide, and (2) the antigen is administered. Examiner Wilson suggested that claims 64, 67, 68, 70, 72, 74, 76, and 90 be amended to recite an affirmative step of administering the nucleic acid, wherein both steps together induce an immune response, and to replace "effective to induce the immune response" with a recitation that "an immune response to said antigen is induced in the individual." Finally, Examiner Wilson indicated that he would withdraw the rejection of claims 24, 27, 28, 95, 98, 99, 108, 111, and 112 for indefiniteness, since only "a" motif is recited in these claims.

Further details of the remarks made by Applicant and Applicant's representatives are presented hereinbelow.

A. Rejections Under 35 U.S.C. § 112

1. The Rejection Under 35 U.S.C. § 112, first paragraph

Claims 19, 21-28, 63-78, 90, 92-103, and 105-114 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Examiner contends that the term "derived" (claims 19, 63, 65, 69, 71, 73, 75, and 103) does not have support on pages 5-6 as cited by Applicant, and the specification only contemplates saponins obtained, not derived, from *Quillaja saponaria*. Applicant respectfully disagrees. On page 5, lines 16-18, the specification recites that "[t]he invention encompasses the saponin *per se*, as well as natural and pharmaceutically acceptable salts and pharmaceutically acceptable derivatives." Furthermore, claim 2 as originally filed recites that "the saponin adjuvant is derived from *Quillaja saponaria*." (emphasis added.) The original claims are deemed part of the disclosure of the application. See M.P.E.P. § 2163.06 (Eighth Edition, August 2001, revised February 2003) (citing In re Benno, 768 F.2d 1340 (Fed. Cir. 1985)). As such, the term "derived" is fully supported in the specification on page 5, lines 16-18, and claim 2 as originally filed.

The Examiner contends that the phrase "phosphate-modified nucleotides" (claims 25, 65, 66, 96, 97, and 110) does not have support in the paragraph bridging pages 9-10 as stated by Applicant. The Examiner alleges that the citation in the specification only discusses modifying the 5′ or 3′ nucleotides of an oligonucleotide with phosphorothioate-modified nucleotides, which is not equivalent to "phosphate-modified nucleotide" as claimed.

Applicant respectfully disagrees with the Examiner. However, merely to expedite prosecution of the application, Applicant has amended the claims to replace "phosphate-modified nucleotides" with a Markush group of specified chemical groups. The support for the amendment can be found, *e.g.*, on page 9, line 14, to page 10, line 9 of the instant specification; the specification is clearly not limited to what the Examiner contends.

The Examiner contends that the specification does not support administering a nucleic acid sequence encoding an antigen as claimed (claims 64, 67, 68, 70, 72, 74, 76, 80, 90, and 103). The Examiner alleges that the citation (page 14, line 22, to page 15, line 4) does not state the nucleic acid sequence is administered to the individual or test system or that the nucleic acid sequences suitable for the enhanced immune response are suitable for putting into the immune adjuvant and administering to an individual or test system.

Applicant respectfully disagrees. Firstly, Applicant points out that, according to applicable case law, "*ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question." Fujikawa v. Wattanasin, 93 F.3d 1559, 39 USPQ 2d 1895, 1904 (Fed. Cir. 1996); see also, Application of Edwards, 568 F.2d 1349, 1351-1352 (C.C.P.A. 1978); Application of Smythe, 480 F.2d 1376, 1384 (C.C.P.A. 1973); and M.P.E.P. § 2163.02. In Application of Smythe, the Court of Customs and Patent Appeals explained:

> A hypothetical situation may make our point clear. If the original specification of a patent application on the scales of justice disclosed only a 1-pound "lead weight" as a counterbalance to determine the weight of a pound of flesh, we do not believe the applicant should be prevented, by the so-called "description requirement" of the first paragraph of § 112, or the prohibition against new matter of § 132, from later claiming the counterbalance as a "metal weight" or simply as a 1-pound "weight," although both "metal weight" and "weight" would indeed be progressively broader than "lead weight," including even such as undisclosed, but obviously art-recognized equivalent, "weight" as a pound of feathers. The broader claim language would be permitted because *the description of the use and function* of the lead weight as a scale counterbalance in the *whole disclosure* would immediately convey to any person skilled in the scale art the knowledge that the applicant invented a scale with a 1–pound counterbalance weight, regardless of its composition.

Id. at 1384 (emphasis in original). See also, M.P.E.P. p2100-17.

Secondly, the instant specification explicitly teaches, and thus does support, the administration of a nucleic acid encoding an antigen. The specification repeatedly discloses administration of an antigen. For example, on page 12, lines 8-12, the specification discloses that "the invention is directed to a method for increasing the immune response to an antigen in an individual or a test system to which the antigen is administered …." On page 16, lines 12-15, the specification discloses that "a fourth aspect of the invention encompasses a method of stimulating immunity to an antigen in an individual comprising administering an effective amount of a vaccine composition comprising an antigen, …." On page 18, lines 9-11, the specification discloses that "the composition may be given as a single injection of a mixed formulation of saponin, oligonucleotide, and antigen …." The specification discloses various examples of an "antigen" as a protein, a peptide, a polysaccharide, a lipid, a glycolipid, a phospholipid, or "a nucleic acid encoding the

antigenic protein or peptide of interest" (see page 14, line 22 to page 15, line 1, of the instant specification). It is also evident from the specification that the reference in the specification to the nucleic acid as an example of an "antigen" was done for purposes of convenience such that "nucleic acid encoding an antigen" need not be repeated in every context where "antigen" was used in the specification. Thus, the specification clearly supports the administration of a nucleic acid encoding an antigen.

The Examiner contends that the phrase "wherein the nucleic acid encoding the antigen is administering to the individual or test system within 0-2 days of the administration of the immune adjuvant composition" (claim 113) is new matter. The Examiner alleges that the specification does not contemplate administering DNA encoding an antigen and a mixture of saponin and immunostimulatory oligonucleotide together or separately.

Applicant respectfully disagrees. As discussed above, case law and the M.P.E.P. clearly state that literal support is not necessary to satisfy the written description requirement of § 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question.

On page 18, lines 9-11, the instant specification recites that "the composition may be given as a single injection of a mixed formulation of saponin, oligonucleotide, and antigen or as separate injections given at the same site within a short period of time (*i.e.*, 0-2 days)." As discussed above, administration of an "antigen" as that term is used in the specification encompasses administration of a nucleic acid encoding an antigen. Although the specification does not specify the exact combination to be used when saponin, oligonucleotide and antigen are administered separately, there are only 4 possibilities: (1) administer saponin, oligonucleotide, and antigen separately; (2) administer saponin and oligonucleotide together, antigen separately; (3) administer saponin and antigen together, oligonucleotide separately; and (4) administer oligonucleotide and antigen together, saponin separately. This is an extremely small genus, and, in the case of a limited genus, each member is adequately described without specifically naming each species. *Cf.* In re Petering, 301 F.2d 676, 682 (C.C.P.A. 1962) (holding each compound within a class of 20 compounds adequately described by a generic structure). Moreover, since the specification repeatedly teaches saponin and CpG oligonucleotide together in a composition, for example, on page 11, lines 1-2, a person of ordinary skill in the art would understand that the specification contemplates administration of saponin and oligonucleotide together, and antigen separately.

2. <u>The Rejections Under 35 U.S.C. § 112, second paragraph</u>

Claims 19-28, 63-78, 80-83, and 90-116 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicant respectfully disagrees.

According to applicable case law, the requirement of 35 U.S.C. § 112, second paragraph, means that the claims must have a clear and definite meaning when construed in the light of the complete patent document. Standard Oil Co. v. American Cyanamide Co., 774 F.2d 448, 227 U.S.P.Q. 293 (Fed. Cir. 1985). The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Orthokinetic Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (Fed. Cir. 1986). In the present situation, the claims are definite when considering the disclosure of the instant specification for the reasons stated below.

The Examiner contends that claims 64, 67, 68, 70, 72, 74, 76, and 90 are unclear because they do not clearly set forth the steps of the claims required to induce the immune response against the antigen. The Examiner alleges that the claims only require administering the immune adjuvant to induce an immune response against an antigen while administering both the immune adjuvant and the nucleic acid sequence encoding the antigen are required. The Examiner further alleges that the amount of "immune adjuvant" required to induce an immune response against the antigen is not defined in the specification or in the art at the time of filing.

Merely to expedite prosecution of the application, Applicant has amended the above-identified claims to recite an affirmative step of administering the nucleic acid molecule comprising a nucleotide sequence encoding an antigen, wherein the nucleic acid molecule is administered separately from the immune adjuvant composition or in the same formulation with the immune adjuvant composition.

Applicant respectfully disagrees with the Examiner's contention that the amount of "immune adjuvant" required to induce an immune response against the antigen is not defined in the specification or in the art at the time of filing. It is clear from the specification that the amount of immune adjuvant to be used is the amount that can induce an immune response to the antigen encoded by the administered nucleic acid molecule. The claims as amended also recite that "an immune response is induced in the individual." One of skill in the art could readily determine the appropriate amount of immune adjuvant to administer using only routine experimentation, especially in view of knowledge in the art of using QS saponins as immune adjuvant and knowledge in the art of using CpG oligonucleotides as immune adjuvant.

Nevertheless, the claims have been amended to delete "effective to induce the immune response" and instead specify that the administering of the immune adjuvant composition and administering of the nucleic acid molecule induce an immune response to the antigen, consistent with the Examiner's suggestion at the interview of March 16, 2004.

The Examiner contends that the phrase "inducing the immune response in an individual to an antigen" (claims 64, 67, 68, 70, 72, 74, 76, and 90) does not make sense. The Examiner alleges that the phrase "to an antigen" is describing the "immune response," not the "individual." The Examiner further alleges that it is unclear whether "the immune response refers to one particular immune response or to any immune response against an antigen."

Applicant respectfully disagrees with the first basis for this rejection. As discussed during the interview held on May 29, 2003 and the interview held on March 16, 2004, the claims as written make it clear that the immune response is induced in an individual, *i.e.*, the term "in an individual" limits the term "immune response," not the term "antigen."

With respect to the Examiner's questioning of whether "the immune response refers to one particular immune response or to any immune response against an antigen," Applicant has amended the preamble of these claims to recite "an" immune response instead of "the" immune response, such that it is clear the claims refer to any immune response against an antigen.

The Examiner contends that the metes and bounds of what applicants consider "chemically modified" saponins (claims 75 and 77) cannot be determined. The Examiner alleges that it is unclear if the phrase encompasses any saponin isolated from *Quillaja saponaria* by chemical means or if the phrase is limited to saponins chemically modified after being isolated, *i.e.*, it is unclear if the phrase is meant to define a purity of saponin or a structural feature of saponin.

Applicant respectfully disagrees. The specification and knowledge common in the art would lead one of skill in the art to understand that the term "chemically modified" as used in the above-mentioned claims and in the present specification means a chemical modification that is a covalent modification that alters the structure of the saponin. For example, Stedman's Medical Dictionary 27th edition (2000, Lippincott Williams & Wilkens:New York, page 1123) defines a chemical modification as an alteration in structure of a molecule...by chemical means; often by the covalent addition of some reagent. It is clear that one of skill in the art would clearly understand the term to mean as defined above. To interpret "chemically modified" saponin as "saponin isolated from *Quillaja saponaria*

by chemical means" is contrary to the plain art-accepted meaning of the word. Moreover, the instant specification teaches that "chemically modified" saponins are not simply "isolated" or "purified" saponins, but are rather isolated saponins with modified chemical structures. On page 7, lines 13-20, the specification gives examples of a chemically modified saponin as one that is conjugated to a protein, peptide, or small molecule. Following such examples, the specification then defines "partially purified" and "substantially purified" saponins (see page 7, line 21, to page 8, line 5) in a way that makes the difference in meaning between "chemically modified" and "purified" abundantly clear. The specification thus makes it clear that "chemically modified" does not mean "purified" or "isolated" (which is consistent with the art-accepted meaning of "chemically modified"). Moreover, when "purified" is intended, the specification uses the word "purified," *e.g.*, QS-21 V1, V2 are referred to as further purified components (not chemically modified). See page 7, lines 11-12 of the specification. Moreover, chemically modified saponins are known in the art. The instant specification cites U.S. Patent No. 5,583,112 in connection with chemically modified saponins (see page 7, line 13), which patent gives examples of chemically modified saponins that are conjugated to another chemical moiety via the carboxyl group on the glucuronic acid (reference **D08** of record at col. 9, lines 32-49). Thus, contrary to the Examiner's contention, it would be clear to a person of ordinary skill in the art that "chemically modified" does not define the purity of a saponin, but rather, it defines a structural feature of a saponin.

The Examiner contends that claims 24, 27, 28, 95, 98, 99, 108, 111, and 112 are indefinite because the limitations improperly refer back to the "motif" which no longer exists in the parent claims.

Applicant respectfully disagrees. The rejected claims recite "a CpG motif", not "the CpG motif" (emphasis added), and thus do not refer back to the "motif" which no longer exists in the parent claims. However, merely to expedite prosecution of the application, Applicant has amended claims 24, 28, 95, 99, 108 and 112 (but not claims 27, 98 and 111) to delete the phrase "a CpG motif" in accordance with the Examiner's suggestion. Applicant disagrees with the Examiner's suggestion to replace "wherein the ... $5'X_1CGX_23'$..." with "wherein the unmethylated CpG dinucleotide comprises $5'X_1CGX_23'$..." in claims 27, 98 and 111, because a dinucleotide cannot comprise (*i.e.*, consist of at least) four nucleotides.

In view of the foregoing, Applicant respectfully requests that the Examiner withdraw the rejections under 35 U.S.C. § 112.

B. Rejections Under 35 U.S.C. § 102 Over Urban and Sasaki

Claims 75, 76, 113, and 114 stand rejected under 35 U.S.C. § 102(e) as being anticipated by United States Patent No. 6,013,258 ("Urban") as supported by Krieg *et al.*, 1998, *Trends in Microbiology* 6:23-26 ("Krieg"). Claims 75, 76, 113, and 114 also stand rejected under 35 U.S.C. § 102(e) as being anticipated by United States Patent No. 5,808,024 ("Sasaki") as supported by Krieg. Applicant respectfully disagrees with the Examiner's rejections.

Urban discloses delivery of plasmids encoding immunogenic HPV peptides by use of ISCOMS, cage-like structures formed of saponins (Quil A) alone or in combination with cholesterol. The Examiner states that Urban teaches administering a plasmid comprising at least one unmethylated CpG dinucleotide and Quil A (col. 6, line 18). The Examiner further states that Krieg disclosed the inherency of plasmid DNA having an unmethylated CpG dinucleotide. The Examiner alleges that "Quil A is inherently a saponin derived from *Quillaja saponaria* and is 'chemically modified' because has been removed from its natural environment by means of chemistry." See Office Action dated October 27, 2003, page 6, 3rd paragraph.

Sasaki discloses *Moraxella* OMP nucleic acids as a vaccine with QS-21 or Quil A as adjuvant or in an ISCOM preparation. The Examiner states that Sasaki teaches administration of the combination of a plasmid encoding an antigen with QS-21. The plasmid taught in Sasaki, according to the Examiner, inherently contains at least one unmethylated CpG dinucleotide. The Examiner alleges that "QS-21 is inherently derived from Quillaja saponaria and is 'chemically modified' because it has been removed from its natural environment by means of chemistry." See Office Action dated October 27, 2003, page 7, 2nd paragraph.

Applicant respectfully disagrees. Neither Urban nor Sasaki discloses "chemically modified" saponins. As discussed above, a "chemically modified" saponin does not mean the same as a "purified" saponin. Therefore, the disclosure of Quil A or QS-21 (purified saponin) as in Urban and Sasaki does not teach "chemically modified saponins."

Anticipation under 35 U.S.C. § 102 requires that a single piece of prior art discloses each and every element of the claimed invention, either expressly or inherently. See In re Robertson, 169 F.3d 743, 745, 49 U.S.P.Q. 2d 1949, 1950 (Fed. Cir. 1999). Neither Urban nor Sasaki discloses or suggests an immunostimulatory oligonucleotide to be used in

combination with chemically modified saponins; therefore each and every claim limitation has not been met.

In view of the foregoing, Applicant respectfully requests that the Examiner withdraw the rejections under 35 U.S.C. § 102.

C. Rejections Under 35 U.S.C. § 103

Claims 19, 21-27, 63-68, 73-77, 90, 95-98, 100-102, 113, and 114 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Weiner *et al.*, 1997, *PNAS* 94:10833-10837 ("Weiner") in view of Kensil, 1996, *Critical Reviews in Therapeutic Drug Carrier Systems* 13:1-55 ("Kensil"). Claims 19, 21, 24, 25, 27, 28, 65, 67, 69, 70, 73-77, 90, 95-98, 100-102, 113, and 114 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Weiner in view of Kensil. Claims 19, 21-27, 63-68, 71-78, 90, 95-98, 100-102, 113, and 114 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Chu *et al.*, 1997, *Journal of Experimental Medicine* 186:1623-1631 ("Chu") in view of Kensil.

According to the Examiner, Weiner discloses that administration of oligonucleotides 1643 and 1758 increased the humoral immune response in a mouse. The Examiner states that oligonucleotide 1643 has three unmethylated CpG motifs and has a phosphorothioate modified nucleotide, and that oligonucleotide 1758 has unmethylated CpG motifs and is equivalent to SEQ ID NO:1 of the present invention. The Examiner adds that oligonucleotide 1758 has a phosphorothioate modified nucleotide. Weiner does not disclose the combination of such immunostimulatory oligonucleotides and a saponin.

According to the Examiner, Chu teaches administering phosphorothioate oligonucleotide 1826 or 1760 as an adjuvant to increase the IgG2a immune response in a mouse. The Examiner states that phosphorothioate oligonucleotide 1826 or 1760 has unmethylated CpG motifs and 1826 is equivalent to SEQ ID NO:2 of the instant invention. The Examiner admits that there is no suggestion in Chu, however, to combine the phosphorothioate oligonucleotides with QuilA, QS-7, QS-17, QS-18, or QS-21.

According to the Examiner, Kensil teaches the use of the saponin adjuvant QS-7, -17, -18, or -21 in combination with vaccines for an adjuvant effect and with other adjuvants to increase the adjuvant effect. The Examiner contends that it would have been obvious to combine the two known adjuvants (the immunostimulatory oligonucleotide containing unmethylated CpGs of SEQ ID NO: 1 or SEQ ID NO: 2 and QS-7, -17, -18, or -21), particularly in light of a teaching in Weiner that provides an invitation to experiment with combinations of immunostimulatory oligonucleotides with other adjuvants.

Applicant respectfully disagrees. Assuming, *arguendo*, that the cited references did make a *prima facie* case of obviousness, Applicant has demonstrated the unexpected result of synergism of CpG oligonucleotides and QS saponins, thereby rebutting any *prima facie* case of obviousness. The Examiner agrees that Applicant has shown unexpected results with the specific combination of QS-21 and phosphorothioate oligonucleotides 1758 (page 17, lines 14-15 of the Office Action mailed July 26, 2001) and 1826 (page 14, lines 1-2 of the Office Action mailed February 12, 2002). The Examiner, however, questions the generalizablity of these results to the genus of CpG oligonucleotides and the genus of QS saponins, and deemed Applicant's arguments filed July 31, 2003 regarding this issue not persuasive.

The Examiner's attention is invited to the Declaration of Dr. Charlotte Kensil under 37 C.F.R. § 1.132, submitted herewith ("Declaration"), discussed below, which addresses the issue of why synergy in immune adjuvant activity is a general attribute of the genus of CpG oligonucleotides and the genus of the QS saponins.

The Examiner's attention is also invited to the applicable case law. In In the Matter of the Application of Kollman, 595 F.2d 48 (C.C.P.A. 1979), the Court of Customs and Patent Appeals states that:

> We feel that the unobviousness of a broader claimed range can, in certain instances, be proven by a narrower range of data. Often, one having ordinary skill in the art may be able to ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof. The proof, thus considered, might then be sufficient to rebut a PTO holding of *prima facie* obviousness.

Id. at 56. In paragraph 6 of the Declaration, Dr. Kensil addresses why CpG oligonucleotides are generally expected to act in the same manner with respect to immune adjuvant activity. Dr. Kensil states that this is because CpG oligonucleotides exert their activity through the same receptor and thus share the same mechanism of action. In paragraphs 7-10 of the Declaration, Dr. Kensil addresses why QS saponins generally are expected to exhibit synergy in immune adjuvant activity with CpG oligonucleotides. Dr. Kensil states that this is because QS saponins share structural similarities and there is a correlation of structure with function. The Declaration clearly sets forth a trend in the exemplified data, *i.e.*, synergistic immune adjuvant activity demonstrated by certain CpG oligonucleotides in combination with certain QS saponins, which would allow a person skilled in the art to reasonably extend the probative value thereof to the genus of CpG

oligonucleotides and the genus of QS saponins. Thus, the Declaration provides compelling evidence to rebut the Examiner's holding of *prima facie* obviousness.

In the Declaration, Dr. Kensil further disagrees with the Examiner regarding the remarks made in support of the Examiner's reasoning as to why Applicant's arguments regarding the section 103 rejections, submitted on July 31, 2003, were not persuasive. See paragraphs 12-19 of the Declaration.

In addition to what Dr. Kensil presents in the Declaration, Applicant contends that the Examiner's allegation that Hemmi *et al.*, 2000, Nature 408:740-745 ("Hemmi") was not available to one of skill in the art at the time of invention (a post-filing publication) and thus cannot be relied upon by Applicant (see Office Action dated October 27, 2003, the paragraph bridging page 10 and page 11) is incorrect as a matter of law. Post-filing date evidence can be used to show unexpected properties of an invention. See *e.g.*, Ex Parte LADD, 112 U.S.P.Q. 337 (Pat.& Tr. Office Bd. App. 1955). In Ex Parte LADD, the Patent Office Board of Appeal held that "we are of the opinion that as long as the appellants have disclosed the compound and its utility they may establish by means of data obtained subsequent to the filing of the present application that it possesses unobvious properties as compared to the compounds of the prior art." *Id.* at 338. Here, the utility taught in the specification is using the combination of CpG oligonucleotides and QS saponins as immune adjuvants, the unexpected property is the synergy displayed by such combination. Hemmi is relied upon to show the synergy applies to the genus of CpG oligonucleotides. Thus, the publication date of Hemmi is irrelevant.

In the Office Action dated October 27, 2003, the Examiner also contends that oligonucleotide 2006 was not taught in the specification and therefore cannot be "in accordance with the teaching of the instant specification." (see the Office Action, page 11, last paragraph). Applicant respectfully disagrees. Oligonucleotide 2006 is within the scope of the claims of the instant application and what is taught in the specification because the specification teaches the use of CpG oligonucleotides in general and oligonucleotide 2006 is "an immunostimulatory oligonucleotide comprising at least one unmethylated CpG dinucleotide" as recited in the claims. Thus, it is proper for Applicant to come forward with proof of any and all "ordinary" CpG oligonucleotides. To our knowledge, there is nothing unusual or out of ordinary of oligonucleotide 2006, nor has the Examiner come forward with any basis for thinking so.

The Examiner's attention is invited to Application of Katzschmann, 347 F.2d 620 (C.C.P.A. 1965). In that case, Court of Customs and Patent Appeals states that:

> We do not think it was the intent of section 103 that either the examiner, the board or this court should substitute their own speculations for the factual knowledge of those skilled in the art. Where, as here, an affidavit states facts which are relevant to the ultimate determination of the legal issue arising under section 103, we think it must be given careful evaluation and properly weighed to determine whether it factually rebuts the bases upon which the examiner has predicated his finding of obviousness Thus an affidavit such as that of record here may well shift the burden of proof to the examiner to then come forward with further support for his conclusion that the invention would have been obvious under the conditions stated in section 103.

Id. at 622. Since Dr. Kensil has presented compelling evidence as to why synergy in immune adjuvant activity is a general attribute of the genus of CpG oligonucleotides and of the genus of QS saponins, now the burden of proof has shifted to the Examiner to come forward with further support for his conclusion that the invention would have been obvious under the conditions stated in section 103, if these rejections were to be maintained.

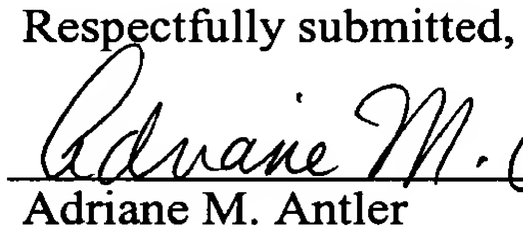
In view of the foregoing, Applicant respectfully requests that the Examiner withdraw the rejections under 35 U.S.C. § 103.

CONCLUSION

Applicant respectfully requests that the amendments and remarks made herein be entered and made of record in the file history of the present application. Withdrawal of the Examiner's rejections and a notice of allowance are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: April 26, 2004



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Enclosures